Pharmacokinetic Properties of a Sufentanil Sublingual Tablet Intended to Treat Acute Pain

Dennis M. Fisher, M.D., Peter Chang, Ph.D., D. Russell Wada, Ph.D., Albert Dahan, M.D., Ph.D., Pamela P. Palmer, M.D., Ph.D.

ABSTRACT

Background: Desirable product attributes for treatment of moderate-to-severe acute pain in many medically supervised settings are rapid onset and a route of administration not requiring intravenous access. The pharmacokinetic characteristics of sublingually administered tablets containing 15 or 30 μg of sufentanil are described.

Methods: Blood was sampled from healthy subjects (four studies, 122 subjects) and patients (seven studies, 944 patients). Studies in healthy subjects determined bioavailability, effect of inhibition of cytochrome P450 3A4, and the plasma concentration profile with single and hourly sublingual doses. Studies in patients evaluated effects of weight, age, sex, and organ impairment on apparent clearance. Noncompartmental and mixed-effect population methods were used.

Results: Bioavailability of a single sublingual tablet was 52%, decreasing to 35% with repeat dosing. Ketoconazole (CYP3A4 inhibitor) increased maximum plasma concentration 19% and increased the area under the curve 77%. After a single 30-μg dose, plasma concentrations reached the published sufentanil analgesic threshold (24 pg/ml) within 30 min, peaked at 1 h, and then decreased below therapeutic concentrations by ~3 h. With hourly administration, plasma concentrations plateaued by the fifth dose. Time for concentrations to decrease 50% from maximal values was similar after 1 dose (2.5 ± 0.85 h) and 12 doses (2.5 ± 0.72 h). Clearance increased with weight, decreased with age, and was not affected by renal or hepatic impairment.

Conclusions: The time course of a single 30-μg dose was consistent with onset of analgesia and redosing frequency observed in clinical trials. Sublingual sufentanil tablets provide the opportunity to noninvasively and rapidly treat moderate-to-severe pain in a monitored setting. **(Anesthesiology 2018; 128:943-52)**

OPIOIDS remain an important part of a multimodal regimen for treatment of moderate-to-severe pain in many acute clinical settings.[1–3] When rapid treatment of acute pain is desired, IV access is usually initiated. There are many patients, such as those in the emergency department, for whom difficulty in obtaining IV access delays the time to obtain pain relief.[4,5] In addition, some patients who require rapid onset of analgesia might not need IV access other than for opioid administration. Oral transmucosal delivery offers a noninvasive route for rapid absorption of lipophilic opioids.[6] However, currently available transmucosal opioid products that contain either fentanyl or buprenorphine are approved for use only in cancer breakthrough pain, opioid addiction treatment, or chronic pain and often contain large doses of opioids not suitable for opioid-naive patients in acute pain.[7–11]

AcelRx Pharmaceuticals (USA) has developed two sublingual sufentanil tablet products: Dsuvia (which consists of a single-dose applicator prefilled with a single 3-mm-diameter 30-μg tablet administered by a healthcare professional no more frequently than hourly) and Zalviso (a patient-controlled analgesia system delivering 3-mm-diameter 15-μg tablets with a 20-min lockout, commercially available in Europe [Grunenthal, Germany]). The two products contain identical ingredients. Once administered under the tongue, the tablets typically dissolve within 5 min, allowing sufentanil to be absorbed transmucosally. The clinical effects and safety of these products have been reported by several investigators.[12–18] We now report the pharmacokinetic characteristics of this sublingual sufentanil tablet formulation and evaluate whether these characteristics are consistent with the clinical profile (onset and offset of analgesia) of sublingual sufentanil tablets reported in published clinical trials.

What We Already Know about This Topic

- Oral transmucosal delivery offers a noninvasive route for rapid absorption of lipophilic opioids
- Available transmucosal fentanyl or buprenorphine products often contain large doses of these opioids and are not suitable for acute use in opioid-naive patients

What This Article Tells Us That Is New

- With sublingual administration of a newly developed 30-μg sufentanil tablet, the time to maximum plasma concentration was approximately 1 h, but the analgesic threshold was typically reached at or before 30 min, which is consistent with the onset of analgesia observed in clinical trials of the 30-μg product
- The time for the plasma concentrations to decrease below the analgesic threshold after a single 30-μg dose was approximately 3 h, which is consistent with the duration of analgesia in those published clinical trials

This article is featured in "This Month in Anesthesiology," page 1A. This is a 2017 Frontiers in Opioid Pharmacotherapy Symposium article.

Submitted for publication August 4, 2017. Accepted for publication January 29, 2018. Corrected on July 27, 2018. From P Less Than, San Francisco, California (D.M.F.); Certara Strategic Consulting, Princeton, New Jersey (P.C., D.R.W.); Leiden University Medical Center, Leiden, The Netherlands (A.D.); and AcelRx Pharmaceuticals, Redwood City, California (P.P.P.).

 Anesthesiology 2018; 128:943-52

<zdoi;10.1097/ALN.0000000000002145>

Materials and Methods

Eleven clinical studies of sufentanil sublingual tablets have been conducted to date: four in healthy subjects (table 1) and seven in postsurgical patients (table 2), in which venous blood was sampled to determine the pharmacokinetic characteristics of sublingual sufentanil. These trials were registered at ClinicalTrials.gov (NCT00612534, NCT01539538, NCT01539642, NCT01639729, NCT01660763, NCT01710345, NCT01721070, NCT01761565, NCT02082236, NCT02356588, and NCT02662556). The dosage strengths evaluated in these trials included Dsuvia (30 μg) and Zalviso (15 μg), as well as tablet prototypes containing 5, 10, and 20 μg of sufentanil administered during phase 2 dose-finding studies. Demographic characteristics are summarized in table 3. All of the studies were approved by either a local or central institutional review board, and all subjects gave informed consent.

After sublingual dosing, the tablet was allowed to dissolve under the tongue and was not to be crushed, chewed, or swallowed. Subjects were not to eat or drink and were to minimize talking for 10 min after tablet administration. With IV administration (studies IAP102 and IAP104), sufentanil was infused over 1 min. For buccal administration (study IAP102), the tablet was placed between the lower gum and lower lip with forceps. For oral administration (study IAP102), subjects swallowed the tablet with approximately 240 ml of distilled water; the subject's mouth was checked to ensure the tablet was swallowed.

Venous blood was sampled, centrifuged at 1,300 *g* for 10 min at 4°C to separate plasma, and then frozen at 20°C within 60 min of collection. Sufentanil plasma concentrations were determined by PRA Early Development Services (Lenexa, Kansas) using a validated assay. In brief, plasma concentration values were determined by liquid chromatography–tandem mass spectrometry after liquid–liquid extraction from 200-μl aliquots with methyl-*tert*-butyl ether under alkaline conditions. Samples were injected onto an API Triple Quad 5,500 mass spectrometer (Applied Biosystems, USA) equipped with UPLC Acquity binary solvent and sample managers (Waters Corporation, USA) after isocratic elution from a Zorbax 300-SCX (3.0 × 50 mm, 5 μm) column (Agilent Technologies, USA) by a mobile phase consisting of 20% 20 mM ammonium formate (pH 2.5) and 80% acetonitrile flowing at 1.00 ml/min. The electrospray source of the spectrometer was in the positive ionization mode. Mass-to-charge ratios of the precursor-to-product ion reactions monitored were 387.2 → 238.1 for sufentanil and 392.2 → 238.2 for the internal standard (sufentanil-D5). Standard curves, analyzed on the same day as study samples, used blank human K2-EDTA plasma spiked to concentrations of 1.00 to 1,000 ng/ml. Inter- and intraassay coefficients of variation over the dynamic assay range (1.000 to 1,000 pg/ml) were less than 7.3% and less than 5.5%, respectively. Three sets of pharmacokinetic analyses were conducted: two using noncompartmental methods and the third using mixed-effect population methods.

Noncompartmental Analyses

Separate analyses were conducted for each of studies SAP101 and IAP104 (analyses of studies IAP101 and IAP102 were published previously[19]). All subjects received 50 mg naltrexone orally twice daily to block the μ-opioid effects of sufentanil. In study SAP101, there were four sequential sufentanil treatment sessions separated by 24 h: 1 × 30-μg IV dose, 1 × 30-μg sublingual dose, 12 × 30-μg sublingual doses at intervals of 60 min, and 2 × 15-μg sublingual doses administered 20 min apart. In study IAP104, a 15-μg sublingual dose was followed by three daily doses of ketoconazole (400 mg each) and a second 15-μg sublingual dose on the day of the final ketoconazole dose; ketoconazole treatment was intended to evaluate the impact of inhibition of cytochrome P450 3A4 (CYP3A4), the enzymatic degradation pathway for sufentanil.

For each sufentanil dose, the maximum plasma concentration and time to maximum plasma concentration were determined by inspection of the data. The area under the

Table 1. Dosing and Sampling Regimen for Trials Conducted in Healthy Subjects

Protocol	No. of Subjects	Regimen, No. of Doses × μg*	Interval between Doses, min	Duration of Sampling, h	Samples/Subject
IAP101	40	1 × 15	—	24	21.9
		40 × 15	20	37	30.6
IAP102†	24	1 × 15	—	24	19.0
		1 × 15 (IV)‡			
		1 × 15 (buccal)			
		1 × 15 (oral)			
IAP104	19	2 × 15§	4,320	24	37.0
SAP101†	39¶	1 × 30 (IV)‡	—	24	20.1
		2 × 15	20	24	18.1
		1 × 30	—	24	18.1
		12 × 30	60	35	32.0

*All doses are sublingual unless otherwise indicated. †Data with intravenous (IV), buccal, and oral administration were excluded from the population pharmacokinetic analysis. ‡The first sample was collected at 1 min. §The second sufentanil dose was preceded by three 400-mg doses of ketoconazole administered at daily intervals. ¶Four subjects were excluded from the population analysis due to incomplete data.

Table 2. Dosing and Sampling Regimen for Trials Conducted in Surgical Patients

Surgery	No. of Patients	Dose, μg	Shortest Time between Doses, min	Longest Duration of Dosing, h	Duration of Sampling, h	Samples/ Patient
Knee replacement	69	5, 10, 15	20	12	12	1
Open abdominal or orthopedic	162	15	20	72	48	1.9
Open abdominal	98	15	20	72	48	1.7
Knee or hip replacement	288	15	20	72	48	1.8
Bunionectomy*	80	20, 30	60	12	12	3.9
Open or laparoscopic abdominal*	107	30	60	48	24	2.9
Mixed surgical population†	140	30	60	12	12	3.8

*Patients in these studies did not have laboratory data to assess the impact of hepatic and renal function on clearance. †Patients requiring at least 24 h of postoperative opioid analgesia.

Table 3. Demographic Characteristics of Subjects/Patients in Pharmacokinetic Trials with Sufentanil Sublingual Tablets

	Healthy Subjects	Surgical Patients
N	122	944
Male/female	58/64	373/571
Age, yr (mean ± SD [range])	29 ± 7 (18–46)	58 ± 14 (18–92)
Weight, kg (mean ± SD [range])	72.1 ± 12.4 (47.8–101.5)	85.0 ± 20.5 (43.0–165.0)

curve from the time of drug administration to the final quantifiable sample, the terminal half-life, and area under the curve extrapolated after the final quantifiable sample were determined using standard methods. The area under the curve from the time of drug administration to the final quantifiable sample was determined using linear trapezoids. Terminal slope was calculated by linear regression of log-transformed values for the final three (or more) detectable plasma concentration values versus time; terminal half-life was 0.693 (log[2]) divided by the terminal slope. The extrapolated area under the curve was determined as the negative of the final detectable plasma concentration value divided by the terminal slope. The total area under the curve was calculated as the sum of area under the curve from the time of drug administration to the final quantifiable sample and the extrapolated area under the curve. The time for plasma concentration to decrease from maximum plasma concentration to one-half maximum plasma concentration (termed plasma half-time) was determined in two studies. For study SAP101, the comparison was between the session in which subjects received a single 30-μg sublingual dose and the final 30-μg sublingual dose of the multidose session. For study IAP104, the comparison was between each sublingual dose (before and after ketoconazole administration).

For study SAP101, bioavailability of the sublingual tablet was calculated as the ratio of the total area under the curve for the single 30-mg sublingual dose compared to IV administration. Bioavailability of a single 30-μg sublingual tablet relative to two 15-μg sublingual tablets administered 20 min apart was calculated as the ratio of total area under the curve for each of these sessions; bioequivalence was evaluated by the 90% CI for the ratio of total area under the curve (and maximum plasma concentration) being contained within 80 to 125%. Bioavailability and bioequivalence point estimates and 90% CIs were calculated from the log-transformed ratios of the values for the two sessions. This comparison was performed for regulatory purposes to allow comparison of safety profiles between patients exposed to the two different sufentanil sublingual tablet strengths. For study IAP104, the effect of ketoconazole was assessed by comparing the log-transformed ratios between post- and preketoconazole values for each of maximum plasma concentration and the total area under the curve.

These analyses were conducted using SAS (version 9.1; SAS Institute, USA). The values are summarized as means (SD) or medians (range). Comparisons between groups was by ANOVA and/or paired *t* tests. Except for time to maximum plasma concentration, terminal half-life, and plasma half-time, comparisons were performed on log-transformed values.

Compartmental Population Analysis

This analysis included plasma concentration data from sublingual administration in all healthy subjects (N = 122) and postsurgical patients (N = 944). A data set suitable for a mixed-effect population analysis was assembled using the R language (http://www.r-project.org, version 3.3.0; accessed May 15, 2016). The analysis was conducted using NONMEM software (version 7.4; Icon Development Solutions, USA).

The base model included two systemic compartments, an absorption rate and absorption lag, a term for bioavailability of the sublingual product compared to IV administration (this term was fixed to the value obtained in a noncompartmental analysis), a term to allow bioavailability to differ between the initial and subsequent sublingual doses, and a term for the effect of ketoconazole on apparent clearance of sufentanil. The model was assumed to be linear with respect to dose and concentration. Interindividual variability was permitted for each of the pharmacokinetic parameters with the exception of bioavailability.

A proportional model was used for residual error between observations and predictions.

Covariates were added to the model in a systematic manner, using a stepwise forward–backward search strategy. Covariates that were evaluated were age, sex, weight, dose level, dose number, and administration of ketoconazole (introduced into the model as a factor). A covariate was included in the model if it decreased the minimum value of the objective function with $P < 0.001$ (10.83 units for the addition of one parameter to the model). This strict inclusion criterion was used to account for multiple hypothesis testing. Hepatic and renal impairment could not be incorporated into the model because aspartate transaminase, alanine transaminase, total bilirubin, and serum creatinine were not assessed in two studies involving surgical patients. Therefore, impact of organ impairment was evaluated using *post hoc* values for clearance (referenced to the upper limit of normal for each assay) in surgical patients for whom laboratory values were available.

The pharmacokinetic model was validated using likelihood profiles. In the first run, all parameters (with the exception of bioavailability with sublingual administration) were estimated. Then for each parameter, that parameter was fixed to a series of values spanning the estimated value. The span was selected so as to ensure that the fit of the model to the data deteriorated, as assessed by the minimum value of the objective function. The results are displayed graphically. The values are reported as means ± SD, median, or range.

Results

Noncompartmental Analysis, Study SAP101

Maximum plasma concentration was markedly lower and time to maximum plasma concentration was later with sublingual compared to IV administration (fig. 1; table 4); total area under the curve was smaller with sublingual administration relative to IV, yielding a bioavailability point estimate of 52% (90% CI, 47 to 57%). In the multidose arm, trough plasma concentration values (obtained before each dose except doses 4 and 6) plateaued by the fifth dose (fig. 2). Repeated sublingual dosing of 30 μg at intervals of 1 h produced a peak plasma concentration 2.4 times that of a single dose. Mean plasma half-time (fig. 3) was similar after a single 30-μg sublingual dose compared to the final (twelfth) dose of the multidose session.

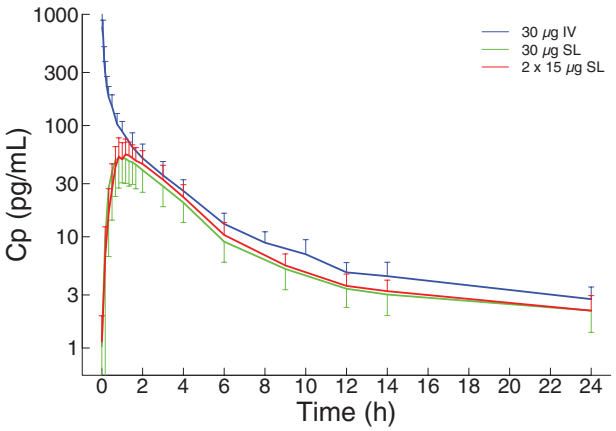

Fig. 1. Plasma concentration profile (mean, SD of venous concentrations) for 30 μg of sufentanil administered to 39 subjects in study SAP101. *Colors* indicate dose and route of administration. Cp = plasma concentration; IV = intravenous; SL = sublingual.

When comparing exposure between the two dosage strengths, referenced to two 15-μg sublingual doses separated by 20 min, a single 30-μg sublingual dose had a relative bioavailability of 89% (90% CI, 81 to 97%) and a point estimate for maximum plasma concentration of 93% (90% CI, 84 to 103%), which jointly met the criteria for bioequivalence.

Noncompartmental Analysis, Study IAP104

After inhibition of CYP3A4 by ketoconazole, maximum plasma concentration increased 19% (90% CI, 3 to 38%; $P = 0.047$), and total area under the curve increased 77% (90% CI, 54 to 101%; $P < 0.001$). Although terminal half-life doubled ($P = 0.003$), plasma half-time increased minimally (0.44 h; 90% CI, −0.10 to 0.97; $P = 0.172$; table 5).

Compartmental Population Analysis

A two-compartment model in which bioavailability decreased with repeat doses of sublingual sufentanil fit the data well (fig. 4). Covariates that were incorporated into the model (table 6) were effects of weight on the systemic parameters; age and administration of ketoconazole on apparent clearance; and a slower absorption rate and lower bioavailability in surgical patients. The addition of each of these covariates was associated with an improvement in the objective function of at least 24 units ($P < 0.00005$ for the addition of one parameter to the model).

Referenced to the median weight of 80 kg, a 1-kg increase in weight increased clearance 0.5% (fig. 5). Clearance decreased 1.6%/yr, referenced to age of 56 yr. Administration of ketoconazole decreased clearance 37.0% (corresponding to a 58.7% increase in the area under the curve). Bioavailability decreased approximately one third with repeated dosing, thereby reducing the impact of accumulation. Absorption was slower in surgical patients compared to healthy subjects. Hepatic and renal impairment did not impact apparent clearance (fig. 6). Likelihood profiles (fig. 7) indicate that each parameter was estimated with precision.

Discussion

After IV administration of 30-μg sufentanil in healthy subjects, mean maximum plasma concentration was more than 1,000 pg/ml, a concentration that is likely to depress

Table 4. Parameters Obtained from the Noncompartmental Pharmacokinetic Analysis of SAP101

Parameter	Treatment			
	1 × 30 μg IV	1 × 30 μg SL	2 × 15 μg SL (20-min interval)	12 × 30 μg SL (60-min intervals)
C_{max}, pg/ml	1,073.94 (968.17)	63.14 (23.49)	66.00 (20.38)	150.78 (36.40)
T_{max}, h	—	1.00 (0.50–2.00)	1.17* (0.67–2.00)	—
$AUC_{0-\infty}$, pg/ml × h	539.68 (113.12)	277.68 (84.36)	307.30 (79.08)	†
Terminal half-life, h	13.72 (6.12)	13.37 (8.89)	15.66 (9.38)	12.68‡ (4.31)
Plasma half-time, h	—	2.5 ± 0.85	—	2.5 ± 0.72
Bioavailability, % (90% CI)	—	52.25 (46.93–57.57)	58.26 (52.94–63.58)	—
Relative bioavailabity, % (90% CI) (*vs.* 2 × 15 μg SL)	—	89 (81–97)	—	—

The values are means (SD) except for T_{max} (median [range]) and bioavailability.

*Referenced to the first dose. †The area under the curve for this session could not be calculated because sampling was limited during certain dosing intervals. ‡After the final (twelfth) dose.

$AUC_{0-\infty}$ = total area under the curve; C_{max} = maximum plasma concentration; IV = intravenous; SL = sublingual; T_{max} = time to maximum plasma concentration.

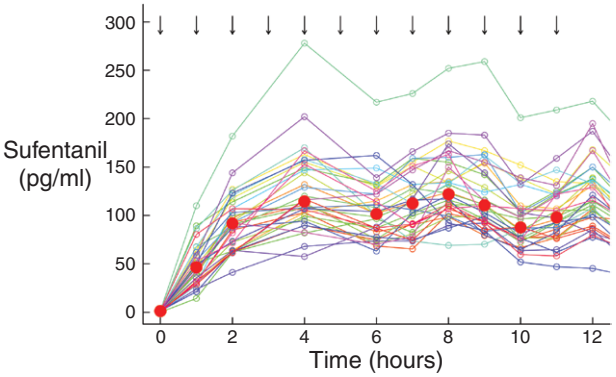

Fig. 2. Trough plasma sufentanil concentrations obtained before each dose (except doses 4 and 6) in the multidose arm of study SAP101 are displayed against time; each *line* represents the values from one subject (N = 34). *Arrows* indicate the times of doses. Median values at each time point are displayed with *large filled red circles*.

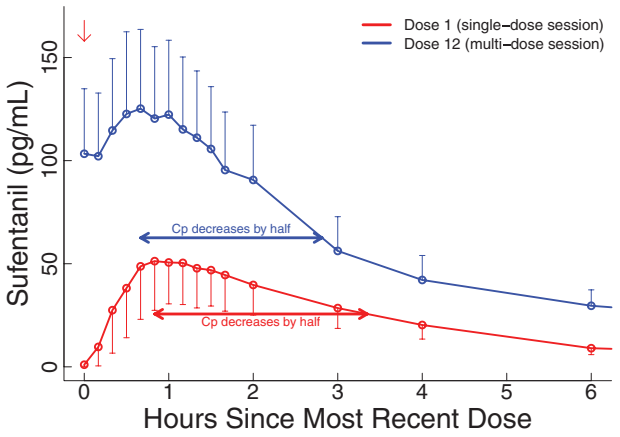

Fig. 3. Plasma concentration profile (mean, SD) after administration of 30-μg sublingual sufentanil tablets in study SAP101. The *red line* displays values from the single-dose session (N = 39). The *blue line* displays values for the final (dose 12, administered as 1-h intervals) of the multidose session (N = 34). *Horizontal arrows* start at the time of the peak plasma concentration and end at one half of that concentration; the *vertical arrow* indicates the dose time. Cp = plasma concentration.

ventilation had subjects not been pretreated with naltrexone. In contrast, the same dose administered sublingual yielded a mean maximum plasma concentration of 63 pg/ml. The lower maximum plasma concentration with sublingual administration results from two factors, bioavailability of 52%, and a slower absorption profile compared to IV. The resulting sublingual plasma concentration profile would likely delay onset of analgesia compared to an IV bolus of 30-μg sufentanil but would do so without incurring a high maximum plasma concentration, thereby minimizing side effects.

Clinical trials that evaluated the analgesic time course after a single 30-μg sublingual sufentanil tablet demonstrated that analgesic onset was typically 15 to 30 min, and repeated doses were required at intervals of ~3 h.[13,16,17] These values can be compared to the plasma concentration profiles obtained in SAP101. After a single 30-μg sublingual sufentanil tablet, plasma concentration exceeded 30 pg/ml by 30 min (fig. 3). Scott *et al.*[20] demonstrated that the equilibration half-life between blood and effect-site concentrations (known as $t_{1/2}k_{e0}$) for sufentanil was 6.2 min; therefore, it is likely that effect site concentrations at 30 min were at least the minimum median effective concentration of sufentanil (24 pg/ml) reported by Lehmann *et al.*[21] By 180 min after administration, plasma concentration decreased to ~30 pg/ml, consistent with a typical 3-h dosing interval. Thus, the plasma concentration profile after a single dose appears to predict the typical analgesic profile with the 30-μg sublingual sufentanil tablet. Similarly, clinical studies evaluating the 15-μg sublingual sufentanil patient-controlled analgesia system demonstrate an interdosing interval of half this duration, averaging 81 to 100 min.[14,22] Patients can titrate to effect with the 15-μg sublingual sufentanil patient-controlled analgesia system as frequently as every 20 min; therefore, onset of analgesia with the 15-μg dosage strength was not measured.

Table 5. Parameters Obtained from the Noncompartmental Pharmacokinetic Analysis of IAP104 (15-μg Sublingual Sufentanil Tablet)

Parameter	Before Ketoconazole	After Ketoconazole	*P* Value
C_{max}, pg/ml	39.95 ± 18.57	46.00 ± 16.50	0.047
T_{max}, h	0.83 (0.33–2.00)	1.17 (0.67–2.00)	< 0.001
$AUC_{0-\infty}$, pg/ml × h	138.66 ± 64.36	243.92 ± 110.86	< 0.001
Terminal half-life, h	6.35 ± 7.49	13.12 ± 8.31	0.003
Plasma half-time, h	2.36 ± 0.15	2.80 ± 0.28	> 0.05

The values are means ± SD except for T_{max} (median [range]); 400 mg of ketoconazole was administered daily for 3 days between doses of sublingual sufentanil.

$AUC_{0-\infty}$ = total area under the curve; C_{max} = maximum plasma concentration; T_{max} = time to maximum plasma concentration.

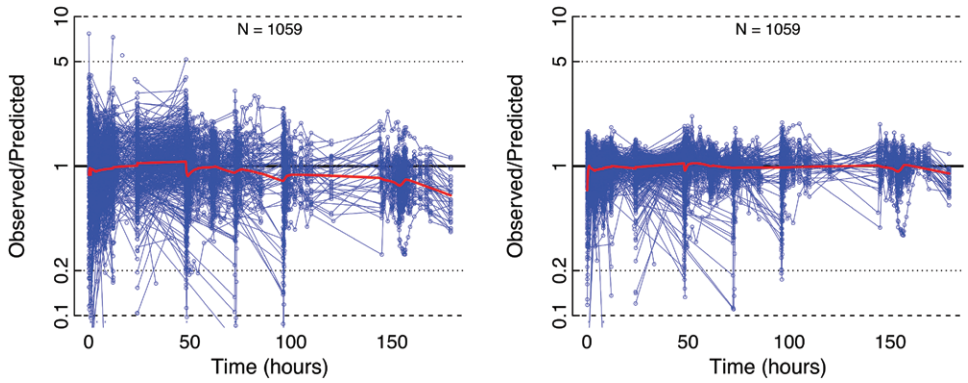

Fig. 4. Goodness-of-fit graphics for the compartmental mixed-effect model. (*Left*) Population fit. (*Right*) *Post hoc* fit. Each *line* represents the ratio of observed to predicted values for one subject *versus* time (h). The *red line* is a smoother (Supersmoother); for both the population and *post hoc* fit, it tracks the line of identity, indicating that the model is unbiased.

Table 6. Pharmacokinetic Parameters from the Compartmental Population Analysis

Parameter	Estimate	Interindividual Variability*
WTFCTR (weight factor)	$(KG†/80)^{0.4058}$	—‡
AGEFCTR (age factor)	1 – 0.01628 × (AGE§ – 56)	—‡
KETOFCTR (factor for ketoconazole)		—‡
In the absence of inhibition	1.0	
In the presence of inhibition	0.629931	
Clearance, l/h	38.36 × WTFCTR × AGEFCTR × KETOFCTR	0.3192
Central volume, l	47.05 × WTFCTR	0.9258
Distribution Clearance, l/h	33.32 × WTFCTR	0.3631
Peripheral volume, l	670.8 × WTFCTR	0.5751
Absorption rate, per h		0.1179
Healthy subjects	0.5007	
Patients	0.3591	
Absorption lag, h	0.06823	—‡
Relative bioavailability		—‡
Healthy subjects	1.0	
Patients	0.8156	
Sublingual bioavailability		—‡
Initial doses	0.531‖	
Repeat doses (> 2)	0.350	

*Calculated as the sqrt($OMEGA^2$), where $OMEGA^2$ is the variance of interindividual variability. †KG is weight in kg (one subject whose weight was missing was assigned the median weight of 80 kg). ‡Interindividual variability was not permitted for this parameter in the optimal model. §AGE is age in yr; median age is 56 yr. ‖This 0.531 value, which differs slightly from the geometric mean ratio value from an ANOVA model in table 4 (0.5225), was fixed to the median individual bioavailability determined in the noncompartmental analysis of the single sublingual 30-μg dose in study SAP101.

Several factors influence systemic exposure to sublingual sufentanil (assessed by apparent clearance, total area under the curve, or maximum plasma concentration). Older and lighter-weight subjects had a lower clearance compared to younger and heavier subjects. Administration of ketoconazole, a potent inhibitor of the CYP3A4 elimination pathway, yielded a small increase in maximum plasma concentration and a larger increase in total area under the

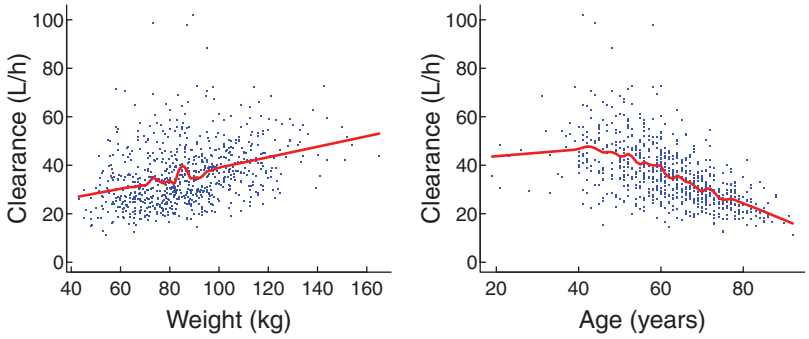

Fig. 5. Individual (*post hoc*) estimates for clearance from the optimal population pharmacokinetic model are displayed against weight (*left*) and age (*right*). The *red line* is a smoother (Supersmoother).

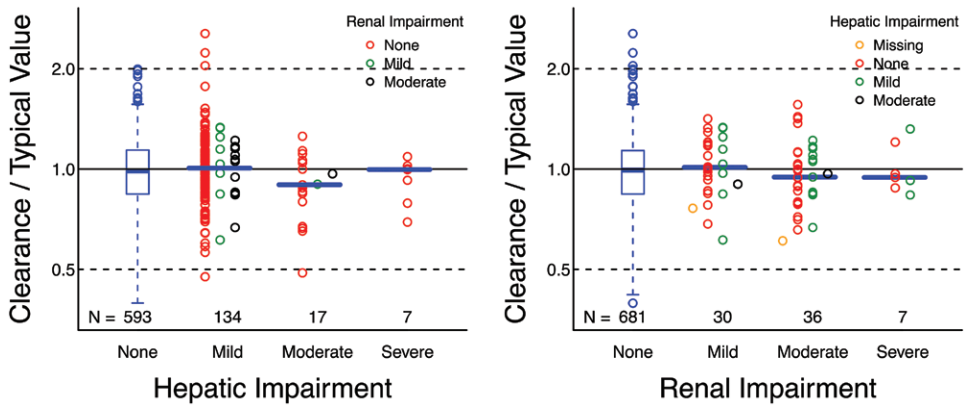

Fig. 6. The ratio of values for clearance to the typical value (log scale) are displayed as a function of hepatic (*left*) and renal impairment (*right*) in surgical patients (excluding subjects from two studies). For subjects with normal hepatic or renal function, values are displayed as a box plot. For the other groups, individual values are displayed as *circles*, color-coded to indicate whether subjects with hepatic impairment had renal impairment and *vice versa*; the median value is displayed with a *horizontal line*. For each of aspartate transaminase, alanine transaminase, total bilirubin, and serum creatinine, "normal" was defined as a value less than the upper limit of normal for that test. For alanine transaminase and aspartate transaminase, "mild" was defined as a value greater than the upper limit of normal but less than or equal to three times the upper limit of normal; "moderate" was defined as value greater than three times the upper limit of normal but less than or equal to five times the upper limit of normal; and "severe" was defined as a value greater than five times the upper limit of normal. For bilirubin, "mild" was defined as a value greater than the upper limit of normal but less than or equal to 1.5 times the upper limit of normal; "moderate" was defined as a value more than 1.5 times the upper limit of normal but less than or equal to three times the upper limit of normal; and "severe" was defined as greater than three times the upper limit of normal. For each subject, the most severe of these individual criteria was used to define "hepatic impairment." Renal impairment was based on serum creatinine and glomerular filtration rate calculated with the Cockcroft–Gault equation ("normal": creatinine less than upper limit of normal; "mild": creatinine greater than upper limit of normal and glomerular filtration rate greater than 60 ml/min; "moderate": glomerular filtration rate between 30 and 60 ml/min; and "severe": glomerular filtration rate at most 30 ml/min).

curve after a single dose of sublingual sufentanil; in the compartmental analysis, ketoconazole decreased sufentanil clearance by ~37%. If sublingual sufentanil tablets were administered at a fixed interval (as was the case in studies in healthy subjects), both maximum plasma concentration and the area under the curve would be higher in subjects who were elderly or lighter-weight or who took an inhibitor of CYP3A4. However, the proposed dosing regimen for both sublingual sufentanil tablet products is on an "as needed" basis, which should minimize the impact of the factors that influence systemic exposure.

With some drugs, repeated administration leads to marked increases in the time for plasma concentration to decrease to one half of maximum plasma concentration compared to values with a single dose.[23] This measurement was termed "context-sensitive half-time" and was developed to quantify the time after the end of a continuous infusion that plasma concentration decreases from the value at end-infusion (maximum plasma concentration) to one half of maximum plasma concentration.[24] We applied a similar concept to our data, determining the time from time to maximum plasma concentration after the final dose to plasma concentration reaching one half of maximum plasma concentration (termed "plasma half-time") after a single dose *versus* the last of 12 doses. Although maximum plasma concentration was higher after the final 30-μg dose in the multidose arm of SAP101 compared to the single-dose arm, the time to reach one half of maximum plasma concentration

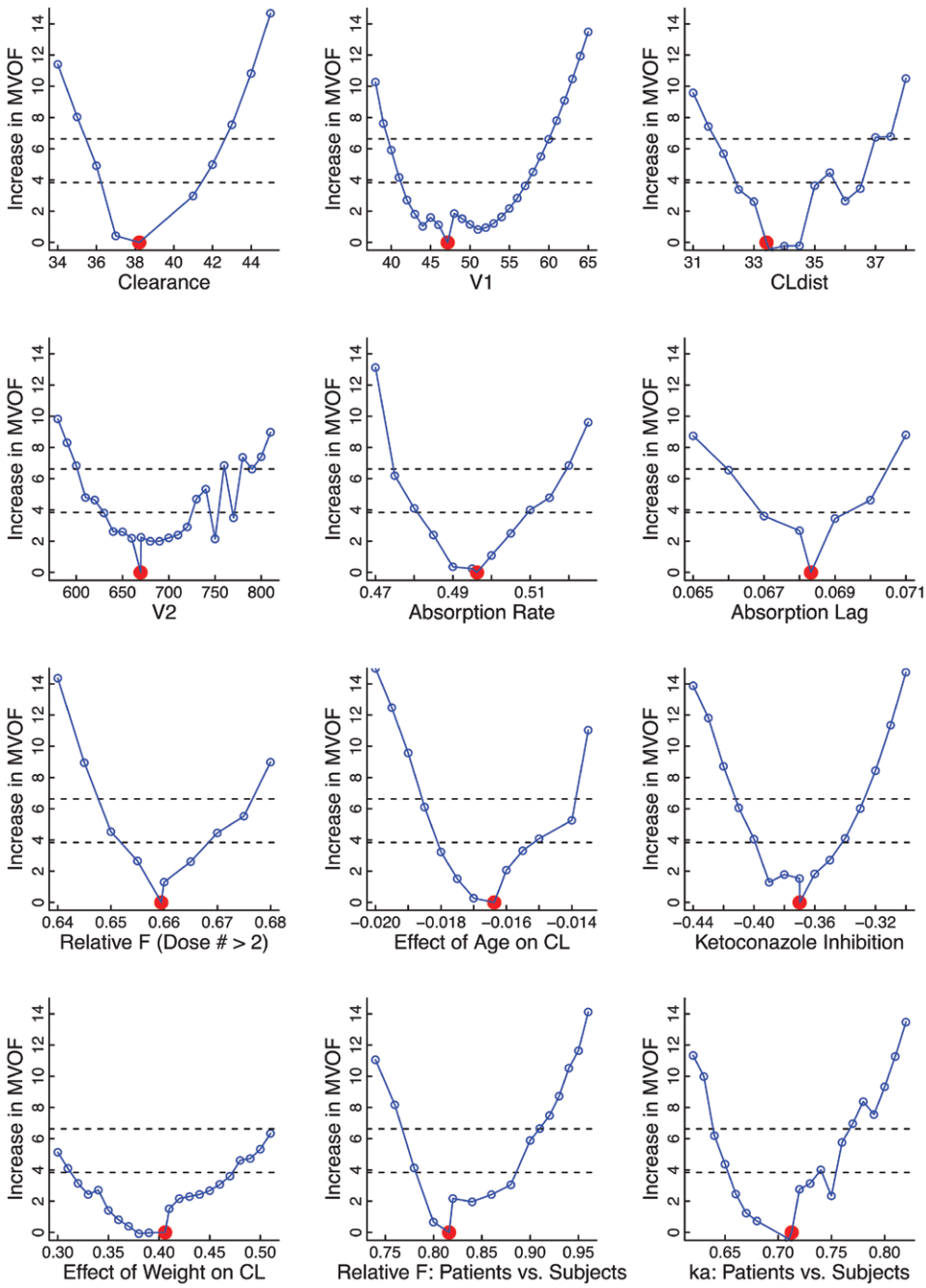

Fig. 7. Likelihood profiles are displayed for each parameter estimated in the population pharmacokinetic analysis. The *x* axis shows the values estimated (*red circle*) or fixed (*blue circles*) in the analysis. The *y* axis shows the change in the minimum value of the objective function (MVOF) compared to the NONMEM run in which the value for that parameter is estimated. *Dashed horizontal lines* mark increases of 3.84 and 6.64 in the minimum value of the objective function, associated with *P* values of 0.05 and 0.01, respectively. CL = clearance; CLdist = distribution clearance; F = relative bioavailability; ka = absorption rate; V1 = central volume.

did not differ between the single dose and the twelfth dose. Willsie *et al.*[19] reported similar results for 15-μg sublingual sufentanil tablets in study IAP101 administered at intervals of 20 min: plasma half-time was 2.2 h after a single dose and 2.5 h after the fortieth dose ($P > 0.05$ by paired *t* test). Inhibition of CYP3A4 in study IAP104 increased plasma half-time minimally, despite a large increase in area under the curve and doubling of terminal half-life (table 5).

Repeated administration of 30-μg sublingual sufentanil tablets at intervals of 1 h in healthy subjects (study SAP101) was associated with increasing plasma concentration *versus* time: plasma concentration peaked at two to three times that of a single dose and trough plasma concentration values plateaued by the fifth dose. This magnitude of accumulation with repeated hourly administration is likely to overestimate what occurs in clinical practice with the 30-μg tablet. In

patients who received the 30-μg sublingual tablet (in whom repeat dosing was based on their request), the median interdose interval was 3 h,[13,16,17] markedly longer than the fixed 1-h dosing interval in healthy subjects; this longer interdose interval reduces the magnitude of accumulation. Consistent with this, in patients treated with 30-μg sublingual tablets as requested more than 12 h, plasma concentration measured at 1, 4, 8, and 12 h ranged from 30 to 50 pg/ml,[13,16,17] much lower than the maximum plasma concentration achieved with fixed hourly doses in SAP101 (151 pg/ml).

Patients might not follow dosing instructions, so to address what would happen if a subject inadvertently swallows a sufentanil sublingual tablet (rather than allowing for transmucosal administration), study IAP102 was conducted with an arm in which subjects were instructed to swallow the tablet with 240 ml of distilled water. Compared to sublingual administration, swallowed drug yields markedly lower systemic exposure (bioavailability of 9% *vs.* 52%) and a slightly later time to maximum plasma concentration (1.2 h *vs.* 1.0 h).[19] In comparison, swallowed fentanyl has a bioavailability of 31% and a time to maximum plasma concentration of 1.5 h.[25] Fentanyl's higher gastrointestinal bioavailability and later time to maximum plasma concentration could result in late large secondary plasma concentration peaks because a large fraction of fentanyl (50 to 80%) is solubilized in saliva and swallowed during transmucosal delivery.[25] The low bioavailability of sufentanil when the intact tablet is swallowed implies that late large secondary plasma concentration peaks are unlikely to occur with sufentanil sublingual tablets, even if solubilized drug is inadvertently swallowed during transmucosal delivery.

Bioavailability was 18% lower and absorption rate was 30% slower in surgical patients compared to healthy subjects. The lower bioavailability may result from some subjects not following instructions regarding sublingual placement of the tablet. The slower absorption may result from decreased saliva (possibly due to anesthetic drugs such as drying agents) slowing the rate at which sufentanil is solubilized from the tablet. In addition, as evidenced in the noncompartmental analysis for both the SAP101 and IAP101 studies, repeated administration in healthy volunteers is associated with a decrease in bioavailability of sublingual sufentanil; data from the present studies do not provide an explanation of this phenomenon.

Transmucosal delivery of opioids (particularly fentanyl and buprenorphine) is commonplace to treat breakthrough pain in cancer patients, in patients with chronic pain, or patients who require maintenance opioid therapy to treat opioid dependence. To date, no transmucosal opioid products are approved for treatment of moderate-to-severe acute pain in patients who are not tolerant to opioids. Sufentanil was selected for development in an sublingual tablet because it is more potent than fentanyl, thereby permitting the tablet to be extremely small (3-mm diameter), generating minimal salivary response and minimizing swallowed drug. Pharmacokinetic and pharmacodynamic characteristics of sufentanil are similar to fentanyl, but sufentanil may result in less accumulation with repeated administration[23] and has lower bioavailability if the product were inadvertently swallowed. Sufentanil was also selected for its lack of active metabolites (which contrasts with commonly used analgesics such as morphine, hydromorphone, codeine, tramadol, and meperidine).[26] Importantly, clinical trials evaluated safety and clinical effects of sufentanil sublingual tablets in nonopioid tolerant patients (patients using 15 mg or less of oral morphine daily equivalent).[12–18,22] In contrast, approved transmucosal fentanyl products contain opioid doses that are likely to be excessive for patients who are not opioid-tolerant; as a result, these products are approved only for patients who are opioid-tolerant (typically 60 mg or more of oral morphine equivalents).[7,8]

A minor limitation of these studies is that venous, rather than arterial, samples were obtained to determine plasma concentrations of sufentanil. With a nonintravenous route of administration, concentrations are changing relatively slowly, such that differences between arterial and venous values are minimal. However, with intravenous administration (one arm of each of studies IAP102 and SAP101), venous concentrations are likely to underestimate peak arterial values. As a result, our use of venous sampling might have underestimated maximum plasma concentration (and, to a lesser extent, area under the curve) for IV administration, understating the differences between sublingual and IV administration.

The noncompartment and compartmental analyses yielded slightly different estimates for the impact of ketoconazole on the area under the curve: 77% *versus* 59%. This difference results from the different mathematical approaches for the two analyses. Regardless, both analyses indicate that ketoconazole increases the area under the curve markedly.

In summary, we report the pharmacokinetic characteristics of sufentanil sublingual tablets in healthy subjects and patients undergoing painful surgical procedures. Maximum plasma concentration after a single 30-μg sublingual dose was markedly damped compared to the value obtained with the same dose administered IV. With sublingual administration of 30-μg sufentanil, time to maximum plasma concentration was ~1 h, but the analgesic threshold was typically reached at or before 30 min, consistent with the onset of analgesia observed in clinical trials of the 30-μg product. Time for plasma concentration to decrease to the analgesic threshold after a single 30-μg dose was ~3 h, consistent with the duration of analgesia in those trials. Several factors—age, weight, and administration of a CYP3A4 inhibitor—influenced clearance of sufentanil. However, these should have minimal impact on systemic exposure in patients because doses of sufentanil sublingual tablets are administered on an "as needed" basis.

Research Support

Supported by AcelRx (Redwood City, California) and the Clinical and Rehabilitative Medicine Research Program of

the United States Army Medical Research and Materiel Command (Fort Detrick, Maryland) under contract No. W81XWH-15-C-0046.

Competing Interests

Drs. Fisher, Chang, Wada, and Dahan are paid consultants to AcelRx (Redwood City, California). Drs. Chang, Wada, and Fisher conducted the population pharmacokinetic analyses. Dr. Palmer is an employee and shareholder of AcelRx.

Correspondence

Address correspondence to Dr. Palmer: AcelRx Pharmaceuticals, 351 Galveston Drive, Redwood City, California 94063. ppalmer@acelrx.com. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. Garimella V, Cellini C: Postoperative pain control. Clin Colon Rectal Surg 2013; 26:191–6
2. Sutter ME, Wintemute GJ, Clarke SO, Roche BM, Chenoweth JA, Gutierrez R, Albertson TE: The changing use of intravenous opioids in an emergency department. West J Emerg Med 2015; 16:1079–83
3. Chou R, Korthuis PT, Weimer M, Bougatsos C, Blazina I, Zakher B, Grusing S, Devine B, McCarty D: Medication-assisted treatment models of care for opioid use disorder in primary care settings. AHRQ Comparative Effectiveness Technical Briefs. Rockville, Maryland, 2016
4. Witting MD: IV access difficulty: Incidence and delays in an urban emergency department. J Emerg Med 2012; 42:483–7
5. Witting MD, Moayedi S, Brown LA, Ismail A: Predictors and delays associated with the need for advanced techniques for intravenous access. J Emerg Med 2017; 53:172–7
6. Zhang H, Zhang J, Streisand JB: Oral mucosal drug delivery: Clinical pharmacokinetics and therapeutic applications. Clin Pharmacokinet 2002; 41:661–80
7. Actiq [package insert]. North Wales, Pennsylvania: Teva Pharmaceuticals, Inc.; 2016.
8. Fentora [package insert]. North Wales, Pennsylvania: Teva Pharmaceuticals, Inc.; 2016.
9. Subsys [package insert]. Chandler, Arizona: Insys Therapeutics, Inc.; 2016.
10. Suboxone [package insert]. North Chesterfield, Virginia: Indivior, Inc.; 2018.
11. Belbuca [package insert]. Raleigh, North Carolina: BioDelivery Sciences International, Inc.; 2016.
12. Minkowitz HS, Singla NK, Evashenk MA, Hwang SS, Chiang YK, Hamel LG, Palmer PP: Pharmacokinetics of sublingual sufentanil tablets and efficacy and safety in the management of postoperative pain. Reg Anesth Pain Med 2013; 38:131–9
13. Singla NK, Muse DD, Evashenk MA, Palmer PP: A dose-finding study of sufentanil sublingual microtablets for the management of postoperative bunionectomy pain. J Trauma Acute Care Surg 2014; 77(suppl 2):S198–203
14. Ringold FG, Minkowitz HS, Gan TJ, Aqua KA, Chiang YK, Evashenk MA, Palmer PP: Sufentanil sublingual tablet system for the management of postoperative pain following open abdominal surgery: A randomized, placebo-controlled study. Reg Anesth Pain Med 2015; 40:22–30
15. Jove M, Griffin DW, Minkowitz HS, Ben-David B, Evashenk MA, Palmer PP: Sufentanil sublingual tablet system for the management of postoperative pain after knee or hip arthroplasty: A randomized, placebo-controlled study. Anesthesiology 2015; 123:434–43
16. Minkowitz HS, Leiman D, Melson T, Singla N, DiDonato KP, Palmer PP: Sufentanil sublingual tablet 30 mcg for the management of pain following abdominal surgery: A randomized, placebo-controlled, phase-3 study. Pain Pract 2017; 17:848–58
17. Hutchins JL, Leiman DL, Minkowitz HS, Jove M, DiDonato KP, Palmer PP: An open-label study of sufentanil sublingual tablet 30 mcg in patients with postoperative pain. Pain Med 2017 Nov 3 [Epub ahead of print]
18. Miner JR, Rafique Z, Minkowitz HS, DiDonato KP, Palmer PP: Sufentanil sublingual tablet 30 mcg for moderate-to-severe acute pain in the emergency department. Am J Emerg Med 2017 Oct 31 [Epub ahead of print]
19. Willsie SK, Evashenk MA, Hamel LG, Hwang SS, Chiang YK, Palmer PP: Pharmacokinetic properties of single- and repeated-dose sufentanil sublingual tablets in healthy volunteers. Clin Ther 2015; 37:145–55
20. Scott JC, Cooke JE, Stanski DR: Electroencephalographic quantitation of opioid effect: Comparative pharmacodynamics of fentanyl and sufentanil. Anesthesiology 1991; 74:34–42
21. Lehmann KA, Gerhard A, Horrichs-Haermeyer G, Grond S, Zech D: Postoperative patient-controlled analgesia with sufentanil: Analgesic efficacy and minimum effective concentrations. Acta Anaesthesiol Scand 1991; 35:221–6
22. Melson TI, Boyer DL, Minkowitz HS, Turan A, Chiang YK, Evashenk MA, Palmer PP: Sufentanil sublingual tablet system *vs.* intravenous patient-controlled analgesia with morphine for postoperative pain control: A randomized, active-comparator trial. Pain Pract 2014; 14:679–88
23. Shafer SL, Varvel JR: Pharmacokinetics, pharmacodynamics, and rational opioid selection. Anesthesiology 1991; 74:53–63
24. Hughes MA, Glass PS, Jacobs JR: Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. Anesthesiology 1992; 76:334–41
25. Darwish M, Kirby M, Robertson P Jr, Tracewell W, Jiang JG: Absolute and relative bioavailability of fentanyl buccal tablet and oral transmucosal fentanyl citrate. J Clin Pharmacol 2007; 47:343–50
26. Smith HS: Opioid metabolism. Mayo Clin Proc 2009; 84:613–24